

1. A method for identifying a candidate compound as a compound that is useful for the treatment of Alzheimer's disease, said method comprising the steps of:

- (a) providing a Tn65Dn mouse;
- (b) administering a candidate compound to said mouse; and
- (c) measuring the activity of the endocytic pathway, wherein a decrease in said activity, compared to the activity in a Tn65Dn mouse not contacted with said candidate compound, identifies said candidate compound as a compound that is useful for the treatment of Alzheimer's disease.

2. The method of claim 1, wherein said activity of the endosomal pathway is selected from the group consisting of endosomal fusion, endosomal recycling, expression of MPR46, accumulation of lysosomal hydrolases in early endosomes, and accumulation of A $\beta$  in early endosomes.

3. A method for identifying a candidate compound as a compound that is useful for the treatment of Alzheimer's disease, said method comprising the steps of:

- (a) providing a Tn65Dn mouse;
- (b) administering a candidate compound to said mouse; and
- (c) measuring A $\beta$  formation, wherein a decrease in said A $\beta$  formation, compared to A $\beta$  formation in a Tn65Dn mouse not contacted with said candidate compound, identifies said candidate compound as a compound that is useful for the treatment of Alzheimer's disease.

4. A method for identifying a candidate compound as a compound that is useful for the treatment of Alzheimer's disease, said method comprising the steps of:

- (a) providing a cell from a Tn65Dn mouse or a cell from a human with trisomy 21;
- (b) contacting said cell with the candidate compound; and
- (c) measuring the activity of the endocytic pathway, wherein a decrease in said activity, compared to the activity in a control cell not contacted with said candidate compound, identifies the candidate compound as a compound that is useful for the treatment of Alzheimer's disease.

5. The method of claim 4, wherein said activity of the endosomal pathway is selected from the group consisting of endosomal fusion, endosomal recycling, expression of MPR46, accumulation of lysosomal hydrolases in early endosomes, and accumulation of A $\beta$  in early endosomes.

6. The method of claim 4, wherein said cell is from a cell line derived from said mouse or said human.

7. The method of claim 6, wherein said cell line is selected from the group consisting of a fibroblast cell line, a neuronal cell line, and a neuroblastoma cell line.

8. The method of claim 4, wherein said cell is selected from the group consisting of a fibroblast, a neuron, and an endothelial cell.

9. The method of claim 4, wherein said cell is *in vitro*.

10. A method for identifying a candidate compound as a compound that is useful for the treatment of Alzheimer's disease, said method comprising the steps of:

- (a) providing a cell from a Tn65Dn mouse or a cell from a human with trisomy 21;
- (b) contacting said cell with the candidate compound; and
- (c) measuring A $\beta$  formation, wherein a decrease in said A $\beta$  formation, compared to A $\beta$  formation in a control cell not contacted with said candidate compound, identifies the candidate compound as a compound that is useful for the treatment of Alzheimer's disease.

11. The method of claim 10, wherein said activity of the endosomal pathway is selected from the group consisting of endosomal fusion, endosomal recycling, expression of MPR46, accumulation of lysosomal hydrolases in early endosomes, and accumulation of A $\beta$  in early endosomes.

12. The method of claim 10, wherein said cell is from a cell line derived from said mouse or said human.

13. The method of claim 12, wherein said cell line is selected from the group consisting of a fibroblast cell line, a neuronal cell line, and a neuroblastoma cell line.

14. The method of claim 10, wherein said cell is selected from the group consisting of a fibroblast, a neuron, and an endothelial cell.

15. The method of claim 10, wherein said cell is *in vitro*.

16. A method for identifying a candidate compound as a compound that is useful for the treatment of Alzheimer's disease, said method comprising the steps of:

- (a) providing a cell expressing a recombinant nucleic acid that increases activity of the endocytic pathway;
- (b) contacting said cell with a candidate compound; and
- (c) measuring said activity, wherein a decrease in said activity, relative to the activity of the endocytic pathway in a cell expressing the recombinant nucleic acid but not contacted with the candidate compound, identifies the candidate compound as a compound that is useful for the treatment of Alzheimer's disease.

17. The method of claim 16, wherein said activity of the endosomal pathway is selected from the group consisting of endosomal fusion, endosomal recycling, expression of MPR46, accumulation of lysosomal hydrolases in early endosomes, and accumulation of A $\beta$  in early endosomes.

18. The method of claim 16, wherein said recombinant nucleic acid encodes a polypeptide selected from the group consisting of rab5, 46 kDa mannose 6-phosphate receptor, and cathepsin D.

19. The method of claim 16, wherein said cell is from a cell line selected from the group consisting of a fibroblast cell line, a neuronal cell line, and a neuroblastoma cell line.

20. The method of claim 16, wherein said cell is selected from the group consisting of a fibroblast, a neuron, and an endothelial cell.

21. The method of claim 16, wherein said cell is *in vitro*.

22. A method for identifying a candidate compound as a compound that is useful for the treatment of Alzheimer's disease, said method comprising the steps of:

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- (a) providing a cell expressing a recombinant nucleic acid that increases activity of the endocytic pathway;
- (b) contacting said cell with a candidate compound; and
- (c) measuring A $\beta$  formation, wherein a decrease in A $\beta$  formation, relative to A $\beta$  formation by a cell expressing the recombinant nucleic acid but not contacted with the candidate compound, identifies the candidate compound as a compound that is useful for the treatment of Alzheimer's disease.

23. The method of claim 22, wherein said recombinant nucleic acid encodes a polypeptide selected from the group consisting of rab5, 46 kDa mannose 6-phosphate receptor, and cathepsin D.

24. The method of claim 22, wherein said cell is from a cell line selected from the group consisting of a fibroblast cell line, a neuronal cell line, and a neuroblastoma cell line.

25. The method of claim 22, wherein said cell is selected from the group consisting of a fibroblast, a neuron, and an endothelial cell.

26. The method of claim 22, wherein said cell is *in vitro*.

27. A method for identifying a candidate compound as a compound that is useful for the treatment of Alzheimer's disease, said method comprising the steps of:

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- (a) providing a mouse expressing a transgene comprising a recombinant nucleic acid that increases activity of the endocytic pathway;
  - (b) administering a candidate compound to said mouse; and
  - (c) measuring said activity, wherein a decrease in said activity, relative to activity in a mouse expressing said transgene but not contacted with said candidate compound, identifies the candidate compound as a compound that is useful for the treatment of Alzheimer's disease.

28. The method of claim 27, wherein said activity of the endosomal pathway is selected from the group consisting of endosomal fusion, endosomal recycling, expression of MPR46, accumulation of lysosomal hydrolases in early endosomes, and accumulation of A $\beta$  in early endosomes.

29. The method of claim 27, wherein said recombinant nucleic acid encodes a polypeptide selected from the group consisting of rab5, 46 kDa mannose 6-phosphate receptor, and cathepsin D.

30. A method for identifying a candidate compound as a compound that is useful for the treatment of Alzheimer's disease, said method comprising the steps of:

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- (a) providing a mouse expressing a transgene comprising a recombinant nucleic acid that increases activity of the endocytic pathway;
  - (b) administering a candidate compound to said mouse; and
  - (c) measuring A $\beta$  formation, wherein a decrease in said A $\beta$  formation, relative to A $\beta$  formation in a mouse expressing said transgene but not contacted with said candidate compound, identifies the candidate compound as a compound that is useful for the treatment of Alzheimer's disease.

31. The method of claim 30, wherein said recombinant nucleic acid encodes a polypeptide selected from the group consisting of rab5, 46 kDa mannose 6-phosphate receptor, and cathepsin D.

32. A method for identifying a candidate compound as a compound that is useful for the treatment of Alzheimer's disease, said method comprising the steps of:

- (a) providing a non-human animal;
- (b) administering to said animal a compound that induces lysosomal dysfunction;

(c) administering to said animal a candidate compound; and  
(d) measuring neurodegeneration in said animal, wherein a decrease in neurodegeneration, relative to an animal administered said compound that induces lysosomal dysfunction but not said candidate compound, identifies the candidate compound as a compound that is useful for the treatment of Alzheimer's disease.

33. The method of claim 32, wherein said compound that induces lysosomal dysfunction is a lysosomal protease inhibitor.

34. The method of claim 32, wherein said animal has increased endocytic pathway activity relative to a normal animal.

35. The method of claim 34, wherein said animal is a Tn65Dn mouse or a mouse expressing a transgene comprising a recombinant nucleic acid that increases activity of the endocytic pathway.